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(54) Title: IBUPROFEN SALT EFFERVESCENT COMPOSITIONS

(57) Abstract

A pharmaceutical powder composition which effervesces when added to water to form a clear aqueous solution for oral administration, is disclosed. The composition comprises: a water soluble pharmaceutically acceptable salt of a 2-(4-isobutylphenyl)propionic acid, as either enantiomer separately or any mixture thereof, in intimate admixture with pharmaceutically acceptable couple comprising at least one acid component and at least one carbonate component, the couple producing carbon dioxide in the presence of water; in which 95 % or more of the ibuprofen has a crystal size from 180 microns to 800 microns and further in which the carbonate component is present in an amount from two to six times the amount of the acid component such that the pH of an aqueous solution formed from 1 g of the composition of 100 ml is greater than 5.0. A similar tablet composition is disclosed which additionally comprises a pharmaceutically acceptable surface active agent such as sodium lauryl sulphate and optionally a lubricant. The effervescent composition may optionally comprise additional pharmacologically active ingredients commonly used in cough and cold remedies.

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IBUPROFEN SALT EFFERVESCENT COMPOSITIONS

This invention relates to pharmaceutical powder or tablet compositions for oral administration, comprising water soluble pharmaceutically acceptable salts of 2-(4-isobutylphenyl)propionic acid and stereoisomers thereof. The compositions of the invention effervesce when added to water to form an aqueous solution of the pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid.

Racemic 2-(4-isobutylphenyl)propionic acid, which is also known as ibuprofen, is a well known medicament with anti-inflammatory, antipyretic and analgesic activities. Known uses of 2-(4-isobutylphenyl)propionic acid include the treatment of pain and inflammation in musculoskeletal disorders such as rheumatic disease, and the treatment of pain in a variety of other disorders, for example headache, neuralgia and dysmenorrhoea.

2-(4-Isobutylphenyl)propionic acid contains a single chiral centre at an asymmetrically substituted carbon atom, and therefore exists in two enantiomeric forms: S(+)2-(4-isobutylphenyl)propionic acid (dexibuprofen) and R(-)2-(4-isobutylphenyl)propionic acid. It will be understood that the term 2-(4-isobutylphenyl)propionic acid as used herein includes either enantiomer separately or any mixture thereof including a racemic mixture.

Aqueous solutions of 2-(4-isobutylphenyl)propionic acid salts are convenient in use and are advantageous for those patients, often children and the elderly, who have difficulty in swallowing tablets or capsules.

2-(4-Isobutylphenyl)propionic acid particularly when present in its free acid form or in an aqueous suspension, has an unpleasant taste with a burning sensation in the throat. Therefore, it is an object of the present invention to produce a powder or tablet composition containing a 2-(4-isobutylphenyl)propionic acid salt which effervesces when added to water to produce a clear solution, and which has no unpleasant taste sensation and to provide a simplified method of producing the same.

2-(4-Isobutylphenyl)propionic acid salts may be produced by reaction between 2-(4-isobutylphenyl)-propionic acid and the corresponding base followed by crystallisation of the required salt. For example reacting sodium hydroxide with 2-(4-isobutylphenyl)-propionic acid produces sodium 2-(4-isobutylphenyl)-propionate. The resulting sodium salt is typically a flaky coarse crystalline solid material, which is milled to produce a finer powder having a crystal size typically less than 100 microns. A fine powder was considered necessary for use in simple effervescent compositions as it was believed that a fine powder gave a faster dissolution rate than a material having a larger crystal size which it was thought could not be used directly in simple effervescent compositions.

Such fine powders are known to be formulated into effervescent tablet compositions, for example in compositions described in the applicant's European Patent Application 0228164. However, a disadvantage of using a fine powder in the production of ibuprofen tablets is that once granulated and dried, a fine powder has a tendency to produce a sticky non flowing mass which will not flow freely into tablet dies and can obstruct the dies. Thus an ibuprofen salt which is a

fine powder (<100 microns) is a difficult material to handle particularly when tabletting. Others have also sought to produce satisfactory effervescent compositions of ibuprofen or a salt thereof.

European Patent Application 0351353 (Aesculapuis Pharma) and documents on the public file thereof teach that effervescent compositions comprising particular ranges of ingredients of ibuprofen or its sodium salt, sodium bicarbonate and citric acid should be mixed in a particular manner, not being admixed in a single phase. There is no teaching in this document of use of a particular crystal size of ibuprofen or its sodium salt.

European Patent Application 0369228 (Bayer) discloses a granulated composition requiring various proportions of a water soluble ibuprofen salt, excipient, stabiliser, sodium or potassium carbonate and an acid component. This composition comprises many expensive ingredients for example stabilisers such as water soluble polymers. There is no teaching in this document of use of a particular crystal size of sodium ibuprofen.

European Patent Application 0203768 (Warner Lambert) discloses effervescent compositions comprising a pre-blended mixture of a granulated therapeutic agent having a particle size of between 100 and 600 microns and a component of a first effervescent system having a similar particle size, the pre-blend being mixed with a second effervescent system. The use of two effervescent systems and the pre-blending of the therapeutic agent results in compositions which are expensive and complicated to prepare. The therapeutic agents disclosed include non-steroidal anti-inflammatory drugs such as acetaminophen, aspirin and ibuprofen. However,

it has been found that if ibuprofen is substituted for the acetaminophen which is used in the specific compositions exemplified, the ibuprofen will not dissolve with effervescence in water to form a clear aqueous solution, and ibuprofen will precipitate. Thus compositions described in this document do not provide satisfactory effervescent formulations, when ibuprofen is used as the therapeutic agent.

The applicant's Indonesian Patent Application P-002967 (published on 12 November 1992, corresponding to International Patent Application PCT/EP92/01221) relates to S(+) sodium ibuprofen. Effervescent granule and tablet formulations are disclosed therein. There is no teaching in this document of use of a particular crystal size of sodium ibuprofen.

It is apparent from the above prior art that the problem of obtaining an acceptable clear solution of an a 2-(4-isobutylphenyl)propionic acid salt from an effervescent tablet, granule or powder composition has been known for some time. Yet none of the prior art compositions are entirely satisfactory, as they involve complicated formulation steps, use expensive ingredients and/or simply do not work for ibuprofen.

Surprisingly, and contrary to what would be expected, it has been found that increasing the crystal size of the 2-(4-isobutylphenyl)propionic acid salt above about 180 microns produces, after granulation and drying, a material which can be used successfully to produce an effervescent powder or tablet formulation. Use of the larger sized crystals of the salt has the advantage of removing the need for a pre-milling step, as the flaky coarse crystals of the salt produced by

recrystallisation during its manufacture can be used directly in compositions of the present invention.

Compositions of the present invention also have the advantage of using inexpensive and readily available ingredients which can simply be blended together in intimate admixture in a single step to form powder or tablet compositions, without requiring complicated processing steps.

Aqueous solutions formed by the compositions of the present invention contain negligible amounts of 2-(4-isobutylphenyl)propionic acid as its free acid. Thus, in comparison to prior art compositions which contain ibuprofen as either the solid acid or its aqueous suspension, the unpleasant taste of 2-(4-isobutylphenyl)propionic acid is largely absent from aqueous solutions formed by the compositions of the present invention.

The present invention provides a pharmaceutical powder or tablet composition comprising; a water soluble pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid, as either enantiomer separately or any mixture thereof, in intimate admixture with a pharmaceutically acceptable couple comprising at least one acid component and at least one carbonate component, the couple producing carbon dioxide in the presence of water; in which 95% or more of the 2-(4-isobutylphenyl)-propionic acid salt has a crystal size, as defined hereinafter, from 180 microns to 800 microns; and further in which the carbonate component of the couple is present in an amount from two to six times by weight the amount of acid component of the couple, such that the pH of an aqueous solution formed from 1 g of

the composition in 100 ml of purified water is greater than 5.0.

2-(4-Isobutylphenyl)propionic acid may form salts with organic or inorganic bases in a conventional manner. Particularly suitable salts of 2-(4-isobutylphenyl)propionic acid include, for example, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), aluminium and ammonium salts, salts with suitable organic bases such as alkylamines, N-methyl-D-glucamine and salts with amino acids such as arginine and lysine. It will be readily understood that these salts may also exist as racemates, separate enantiomers or mixtures thereof. The term 2-(4-isobutylphenyl)-propionic acid salt is defined herein as either enantiomer separately or any mixture thereof including a racemic mixture, of all pharmaceutically acceptable salts of 2-(4-isobutylphenyl)propionic acid that are soluble in water. A preferred salt is sodium 2-(4-isobutylphenyl)propionate, more preferably S(-) sodium 2-(4-isobutylphenyl)propionate.

2-(4-Isobutylphenyl)propionic acid and its salts may exist in more than one crystal form and references to them herein include each crystal form and mixtures thereof. 2-(4-Isobutylphenyl)propionic acid and its salts may also exist in the form of solvates, for example hydrates such as the dihydrate, and references to them herein include each solvate and mixtures thereof.

Preferably, the composition of the present invention comprises from about 1% to about 99% (w/w) of the 2-(4-isobutylphenyl)propionic acid salt, more

preferably from about 5% to about 30% (w/w), most preferably from about 5% to about 10% (w/w).

As used herein the term '(w/w)' signifies that the percentages referred to are the percentage weight (or mass) of the ingredient relative to the total weight (or mass) of the composition.

Pharmaceutically acceptable effervescent couples that produce carbon dioxide in the presence of water may comprise one or more of the following pharmaceutically acceptable acids which are solid at room temperature, for example one or more of the organic acids: citric, tartaric, adipic or malic, together with one or more carbonate component which is defined herein as a pharmaceutically acceptable organic or inorganic carbonate salt which is solid at room temperature, such as one or more of any of the following: sodium carbonate, sodium bicarbonate, potassium carbonate and potassium bicarbonate. The effervescent couple may comprise as each component separately one or more acid and/or one or more carbonate salt, provided the separate acid and/or carbonate salt mixtures are blended to be homogeneous. Preferably the composition comprises one acid as the acid component and one carbonate salt as the carbonate component, more preferably one acid component and one carbonate component. The composition may comprise from about 40% to about 99% (w/w) couple ingredients, more preferably from about 50% to about 95% (w/w), most preferably from about 75% to about 95% (w/w).

Water soluble salts of 2-(4-isobutylphenyl)-propionic acid, can react with the acid component of the couple in the presence of water to precipitate 2-(4-isobutylphenyl)propionic acid. Therefore, to minimise

precipitation of 2-(4-isobutylphenyl)propionic acid, the carbonate component and acid component of the couple are present in a respective ratio by weight of from about two to about six, more preferably from about three to about five, most preferably about four.

Preferably, about 95% or more of the 2-(4-isobutylphenyl)propionic acid salt has a crystal size from about 250 microns to about 600 microns, more preferably from about 300 microns to about 500 microns.

Crystal size is defined herein to be the length of a crystal measured along its longest axis. Measurement may be made by any suitable method, for example that described in Example 1, below. The range of crystal sizes of the 2-(4-isobutylphenyl)propionic acid salt can be determined by sieve separation. The crystal sizes can then be measured by microscopic image analysis, in comparison with standards supplied by the National Physics Laboratory.

The pH of an aqueous solution formed from the composition of the present invention at a concentration of about 1 g of the composition in about 100 ml of purified water is greater than about 5.0, more preferably from about 6.0 to about 9.0, most preferably from about 7.0 to about 8.0.

If the composition of the present invention is a tablet, the composition comprises a pharmaceutically acceptable surface active agent preferably from a trace amount to about 10% (w/w), more preferably from about 0.01% to about 5% (w/w), most preferably from about 0.1% to about 1% (w/w). The surface active agent used in the above tablet composition may ionic or non-ionic. Such an agent is present to disperse the active ingredient

within the tablet and to prevent grit forming at the surface of the tablet. The surface active agent may have the function of a lubricant or alternatively a separate lubricant may be added. The surface active agent may be a solid or liquid and one or more surface active agents can be used. A suitable surface active agent, which also acts as lubricant, is sodium lauryl sulphate. Optionally a tablet composition of the present invention comprises from a trace amount to about 10% (w/w) of a separate lubricant, more preferably from about 0.01% to about 5% (w/w), most preferably from about 0.1% to about 1% (w/w).

Further optional ingredients which may be added to a powder or tablet composition of the present invention include; intense sweeteners such as aspartame, or saccharin, flavour components for example mints such as peppermint; colorants for example brilliant blue FC1 or C1 food blue (as identified in the standard colour index book); and to a tablet composition, compression agents such as sorbitol or lactose which increase the hardness of the tablet. The type and quantity of such ingredients are selected to be readily soluble in water, and to minimise the effect on the pH of the aqueous solution formed when compositions of the invention are added to water. Preferably these optional ingredients separately comprise from a trace amount to about 20% w/w of the composition, more preferably from about 0.1% to about 10% w/w of the composition.

A further optional component in the compositions of the present invention is a water scavenging agent to absorb any water remaining after the granulation step and prevent premature effervescence of the composition. Such a water scavenging agent may be sodium or potassium carbonate especially if already present in the

composition as the carbonate component, in which case no additional water scavenging agent need be added.

Effervescent compositions of the present invention may optionally comprise other pharmacologically active ingredients and/or enhancing agents compatible with the 2-(4-isobutylphenyl)propionic acid salt. Thus, for example, the 2-(4-isobutylphenyl)propionic acid salt may be combined with one or more additional pharmacologically active ingredient or ingredients commonly used in cough or cold remedies, selected from; an antihistamine; caffeine and/or another xanthine derivative; a cough suppressant; a decongestant; an expectorant; a muscle relaxant; a further non-steroidal anti-inflammatory drug (hereinafter known as NSAID) other than 2-(4-isobutylphenyl)propionic acid or its salts; and combinations thereof. The type and quantity of such ingredients are selected to be readily soluble in water and to minimise the effect on the pH of the aqueous solution formed when compositions of the invention are added to water.

Suitable antihistamines which are preferably non-sedating include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chloropheniramine, cyproheptadine, dexbromopheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketoifen, lodoxamide, loratidine, levelcubastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyridamine, setastine, tazifylline, temelastine, terfenadine, tripelennamine or tripolidine. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudeoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifensin, potassium

citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

NSAIDs can be classified chemically as derivatives of arylcarboxylic acids, including salicylic and anthranilic acid derivatives; arylalkanoic acids, including arylacetic, arylpropionic, heteroarylacetic, indoleacetic and indenacetic acids; and enolic acids, including pyrazolidinediones and oxicams.

The term NSAID when used herein includes, but is not restricted to, the following compounds and pharmaceutically acceptable salts thereof.

(1) Arylcarboxylic acids: salicylic acid, acetylsalicylic acid, diflunisal, chlorine magnesium trisalicylate, salicylate, benorylate, flufenamic acid, mefenamic acid, meclofenamic acid, niflumic acid;

(2) Arylalkanoic acids: diclofenac, fenclofenac, alcofenac, fentaizac, flurbiprofen, ketoprofen, naproxen, fenorprofen, fenburfen, suprofen, indiprofen, tiaprofen acid, benoxaprofen, pirprofen tolmetin, zomepirac, clopinac, indomethacin, sulindac;

(3) Enolic acids: phenylbutazone, oxyphenbutazone, azapropazone, feprazone, piroxicam, isoxicam, sudoxicam.

Pharmaceutical powder or tablet compositions according to the present invention may be packaged in any conventional means to protect them from moisture, such as aluminium sachets for powder compositions, or aluminium foil strips for tablet compositions. Tablet

compositions may be coated with conventional film or sugar coatings.

The present invention further comprises a method of making the powder or tablet compositions described herein comprising blending in a single step a water soluble pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid, as either enantiomer or any mixture thereof, having a crystal size from 180 microns to 800 microns with a pharmaceutically acceptable couple comprising at least one acid component and at least one carbonate component to produce a uniform intimately mixed composition; followed by the optional step of adding after the blending step any optional ingredients; followed by the further optional step of compressing the composition in a tablet die to produce tablets.

In an optional step of the above method the 2-(4-isobutylphenyl)propionic acid salt and/or the two components of the couple may be pregranulated by any convenient method such as wetting. Initial contact between the two components of the couple may produce some slight effervescence in the mixture, which is useful in the production of tablets as it can improve the compressibility of the resultant composition. The blended composition thus produced can be optionally granulated (for example by a method such as fluidised bed granulation) to produce a more even particle size, reduce agglomeration and make tabletting the composition easier if tablets are being produced.

A further aspect of the invention comprises use of the compositions disclosed herein in the treatment of pain and fever, the compositions comprising a therapeutically effective amount of a water soluble

pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid, as either enantiomer separately or any mixture thereof.

In therapeutic use compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of the 2-(4-isobutylphenyl)propionic acid salt is from about 50 mg to about 2000 mg. The amount of the 2-(4-isobutylphenyl)propionic acid salt is calculated to provide doses equivalent by weight to doses of, for example, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg or 1600 mg (preferably 200 mg or 400 mg) of racemic 2-(4-isobutylphenyl)propionic acid. If a pure enantiomer, such as S(-) sodium 2-(4-isobutylphenyl)propionate, is used then the quantity of the 2-(4-isobutylphenyl)propionic acid salt in each dose may be substantially reduced to have equivalent effect to the above mentioned doses of the racemic acid.

The present invention will now be illustrated by the following non-limiting examples.

Example 1

Pharmaceutical grade ibuprofen (900 kg) [produced by any convenient method], and flakes of B.P. grade sodium hydroxide (185.5 kg) were dissolved in industrial methylated spirit 600 B.P. (3,078 kg) to give coarse flaky crystals of sodium ibuprofen dihydrate (854 kg). The coarse sodium ibuprofen dihydrate crystals were separated from the reaction mixture, dried and used without further purification as an ingredient in the following composition. The crystal shape of sodium ibuprofen was determined by microscopic image analysis to be flat, planar flakes, crystal size being measured

in the plane which appears in the microscopic screen, with the crystals lying flat and 95% of the crystals were found to have a size in the range of 180 microns to 630 microns.

Ingredient	mg/tablet	% w/w
Sodium ibuprofen dihydrate (racemate)	256	11.3
Anhydrous citric acid	400	17.7
Sodium bicarbonate	1600	70.8
Sodium lauryl sulphate	4	0.2
Total	2260	100.0

Sodium ibuprofen dihydrate, citric acid and sodium bicarbonate in the above ratios were sieved into a mixer bowl and intimately mixed. Purified water (1% w/w) was added to the mixture to granulate the mass, which was then dried at 70°C using the fluidised bed method. The granules were sieved, mixed with sodium lauryl sulphate and then blended for 10 minutes. These granules were then poured into tablet dies and compressed into tablets. The tablets produced dissolved in 100 ml of water with effervescence to produce after less than one minute a clear solution which had a palatable taste and no gritty feel in the mouth.

Example 2

Ingredient	mg/tablet	% w/w
Sodium ibuprofen dihydrate (racemate)	512	14.5
Anhydrous citric acid	600	17.1
Sodium bicarbonate	2400	68.2
Sodium lauryl sulphate	8	0.3
Total	3520	100.0

These ingredients were combined in the above ratios using the method described in Example 1 to prepare solid tablets. The sodium ibuprofen dihydrate was produced as described in Example 1 and had a similar crystal size to the sodium ibuprofen dihydrate used in Example 1, measured in a similar manner.

Example 3

Ingredient	mg/tablet	% w/w
Sodium ibuprofen dihydrate (racemate)	128	6.0
Anhydrous citric acid	400	18.8
Sodium bicarbonate	1600	75.0
Sodium lauryl sulphate	4	0.2
Total	2132	100.0

These ingredients were combined in the above ratios using the method described in Example 1 to prepare solid tablets. The sodium ibuprofen dihydrate was produced as described in Example 1 and had a similar crystal size to

the sodium ibuprofen dihydrate used in Example 1, measured in a similar manner.

Example 4

Ingredient	mg/tablet	% w/w
Sodium ibuprofen dihydrate (racemate)	512	11.3
Anhydrous citric acid	800	17.7
Sodium bicarbonate	3200	70.8
Sodium lauryl sulphate	8	0.2
Total	4520	100.0

These ingredients were combined in the above ratios using the method described in Example 1 to prepare solid tablets. The sodium ibuprofen dihydrate was produced as described in Example 1 and had a similar crystal size to the sodium ibuprofen dihydrate used in Example 1, measured in a similar manner.

Example 5

Ingredient	mg/tablet	% w/w
Sodium ibuprofen dihydrate (racemate)	256	11.3
Codeine phosphate	12.5	0.5
Anhydrous citric acid	400	17.6
Sodium bicarbonate	1600	70.4
Sodium lauryl sulphate	4	0.2
Total	2272.5	100.0

These ingredients were combined in the above ratios using the method described in Example 1 to prepare solid tablets. The sodium ibuprofen dihydrate was produced as described in Example 1 and had a similar crystal size to the sodium ibuprofen dihydrate used in Example 1, measured in a similar manner.

Example 6

Ingredient	mg/tablet	% w/w
Sodium ibuprofen dihydrate (racemate)	256	11.2
Pseudoephedrine hydrochloride	30	1.3
Anhydrous citric acid	400	17.4
Sodium bicarbonate	1600	69.9
Sodium lauryl sulphate	4	0.2
Total	2290	100.0

These ingredients were combined in the above ratios using the method described in Example 1 to prepare solid tablets. The sodium ibuprofen dihydrate was produced as described in Example 1 and had a similar crystal size to the sodium ibuprofen dihydrate used in Example 1, measured in a similar manner.

In the Examples 1 to 6, above, the ibuprofen salt was present at a level equivalent to 100 mg (128 mg), 200 mg (256 mg) and 400 mg (512 mg) of ibuprofen (mass of salt in parentheses).

Example 7

	mg/tablet	% w/w
S(-) sodium ibuprofen dihydrate	256	11.3
Anhydrous citric acid	400	17.7
Sodium bicarbonate	1600	70.8
Sodium lauryl sulphate	4	0.2
Total	2260	100.0

These ingredients were combined in the above ratios using the method described in Example 1 to prepare solid tablets. The S(-)sodium ibuprofen dihydrate was produced in a similar manner to that described in Example 1 from pharmaceutical grade S(+)-ibuprofen and had a similar crystal size to the racemic sodium ibuprofen dihydrate used in Example 1, measured in a similar manner. Each tablet of Example 7 comprised 256 mg of S(-)sodium ibuprofen dihydrate (equivalent to 200 mg of S(+)-ibuprofen)..

Examples 8 to 14

The sodium lauryl sulphate ingredient was omitted from each of Examples 1 to 7 respectively, and granules were prepared as described in Example 1 prior to the tablet compression step, to give respective effervescent powder compositions Examples 8 to 14.

Claims

1. A pharmaceutical powder composition, comprising: a water soluble pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid, as either enantiomer separately or any mixture thereof, in intimate admixture with a pharmaceutically acceptable couple comprising at least one acid component and at least one carbonate component, the couple producing carbon dioxide in the presence of water; in which 95% or more of the 2-(4-isobutylphenyl)-propionic acid ingredient has a crystal size from 180 microns to 800 microns and further in which the carbonate component is present in an amount from two to six times by weight the amount of the acid component of the couple such that the pH of an aqueous solution formed from 1 g of the composition in 100 ml of purified water is greater than 5.0.

2. A composition as claimed in claim 1, in which the 2-(4-isobutylphenyl)propionic acid salt is present in an amount from 5% to 30% by weight of the composition.

3. A composition as claimed in any preceding claim, in which the 2-(4-isobutylphenyl)propionic acid salt comprises sodium 2-(4-isobutylphenyl)propionate.

4. A composition as claimed in claim 4, in which the salt is substantially enriched in S(-)sodium 2-(4-isobutylphenyl)propionate.

5. A composition as claimed in any preceding claim, in which the 2-(4-isobutylphenyl)propionic acid salt has a crystal size from 250 microns to 600 microns.

6. A composition as claimed in any preceding claim, comprising from 50% to 95% of effervescent couple ingredients by weight of the composition.

7. A composition as claimed in any preceding claim, in which the couple comprises citric acid as the acid component and sodium bicarbonate as the carbonate component.

8. A composition as claimed in any preceding claim, which forms an aqueous solution having a pH from 6.0 to 9.0 when 1 g of the composition is added to 100 ml of purified water.

9. A composition as claimed in any preceding claim, comprising one or more additional pharmacologically active ingredient or ingredients selected from an antihistamine, a xanthine derivative, a cough suppressant, a decongestant, an expectorant, a muscle relaxant and a non-steroidal anti-inflammatory drug.

10. A composition as claimed in claim 9, in which the further active ingredient or ingredients comprises codeine and/or pseudoephedrine.

11. A tablet composition comprising the ingredients as described in any preceding claim, and further comprising a pharmaceutically acceptable surface active ingredient.

12. A tablet composition as claimed in claim 11, in which the surface active agent is present in an amount from about a trace amount to 10% by weight of the composition.

13. A tablet composition as claimed in either claim 11 or 12, in which the surface active agent comprises sodium lauryl sulphate.

14. A tablet composition as claimed in any of claims 11 to 13, comprising a lubricant.

15. A method of preparing a powder composition as claimed any of claims 1 to 8, comprising blending in a single step a pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid, as either enantiomer separately or any mixture thereof, having a crystal size from 180 microns to 800 microns with a pharmaceutically acceptable couple comprising at least one acid component and at least one carbonate component to produce a uniform intimately mixed composition.

16. A method as claimed in claim 15, comprising the step of adding after the blending step any of the ingredients described in either claim 9 or 10.

17. A method as claimed in either claim 15 or 16 for preparing a tablet composition, comprising the step of adding after the blending step any of the ingredients described in claims 11 to 14, followed by the further step of compressing the composition in a tablet die to produce tablets.

18. Use of a composition as claimed in any of claims 1 to 14, comprising a therapeutically effective amount of a water soluble pharmaceutically acceptable salt of 2-(4-isobutylphenyl)propionic acid, as either enantiomer separately or any mixture thereof, in treating pain and fever.

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/EP 93/03207

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/19 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,92 20334 (THE BOOTS COMPANY PLC) 26 November 1992 see claims 1,2,6,7,13,16-18,20,21 see page 10, line 18 - page 11, line 9 see page 16, line 22 - line 32 see page 17, line 31 - page 18, line 5 see page 18, line 30 - page 19, line 3 see page 20, line 4 - line 12 see example 17 -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 1994	22. 02. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter ional Application No
PCT/EP 93/03207

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9220334	26-11-92	AU-A-	1671192	30-12-92
		CN-A-	1068734	10-02-93